Original Article

A Randomized Trial of Nasopharyngeal-Synchronized Intermittent Mandatory Ventilation Versus Nasopharyngeal Continuous Positive Airway Pressure in Very Low Birth Weight Infants After Extubation

Philippe Friedlich, MD
Chantal Lecart, MD
Robert Posen, DO
Emily Ramicone, MS
Linda Chan, PhD
Rangasamy Ramanathan, MD

OBJECTIVE:
To prospectively compare the incidence of respiratory failure in premature infants randomized to receive either nasopharyngeal continuous positive airway pressure (NPCPAP) or nasopharyngeal-synchronized intermittent mandatory ventilation (NP-SIMV) in the immediate postextubation period.

STUDY DESIGN:
This is a prospective study of very low birth weight (VLBW) infants randomized at the time of extubation to receive either NPCPAP or NP-SIMV in a university-based level III neonatal intensive care unit. Statistical analysis were performed with the Mann-Whitney *U* test for continuous and ordinal variables, and with the χ-squared test or Fisher's exact test for categorical variables.

RESULTS:
A total of 41 VLBW infants were studied; 19 were in the NPCPAP group, and 22 were in the NP-SIMV group. Respiratory failure after extubation in the NP-SIMV group was significantly lower than in the NPCPAP group (5% vs 37%, respectively) ($p = 0.016$). No statistically significant differences between groups with regard to demographics, severity of initial illness and associated complications, time to extubation, ventilatory management before extubation, weight, age, or nutritional status at the time of extubation were noted.

CONCLUSION:
NP-SIMV applied to VLBW infants upon extubation is more effective in preventing respiratory failure than NPCPAP.

A high proportion of very low birth weight (VLBW) infants require mechanical ventilation for prolonged periods because of insufficient respiratory drive, inability to maintain adequate lung volumes, and frequent episodes of apnea and hypoxemia.[1–7] Progress in ventilatory techniques and support has improved the long-term survival and prognosis of these preterm infants.[8–12] Increasingly, the pulmonary management of these infants is directed at minimizing the need for prolonged mechanical ventilatory support to reduce associated complications such as barotrauma, volutrauma, oxygen toxicity, subglottic stenosis, and nosocomial infections. Nevertheless, early discontinuation of mechanical ventilation often presents difficulties due to residual lung damage, apnea, and atelectasis.[8–10] Various techniques have been proposed to insure successful removal of the endotracheal tube. These include gradual lowering of the intermittent mandatory ventilation (IMV) rate, use of continuous positive airway pressure (CPAP), and use of respiratory center stimulants.[11–14]

To date, little consensus exists with regard to extubation methods and their efficacy.[15–23] Recently published data regarding the use of nasopharyngeal CPAP (NPCPAP) in the postextubation period have reported a need for reintubation of ~25% to 40% in low birth weight infants.[20–22] Between 1995 and 1996, our experience with postextubation use of NPCPAP in VLBW infants (birth weight < 1500 gm) has been accompanied by a reintubation rate of 30%. In an effort to further reduce the need for reintubation in this high-risk population, we investigated new methods for noninvasive ventilation. Subsequently, we reported our initial experience with a combination of NPCPAP and synchronized IMV (SIMV).[24]

The purpose of this study was to prospectively compare the incidence of respiratory failure in VLBW infants randomized in the immediate postextubation period to receive either nasopharyngeal SIMV (NP-SIMV) or NPCPAP. Our primary goal was to compare the two groups in terms of respiratory failure at 48 hours postextubation. We hypothesized that VLBW infants extubated to NP-SIMV would have a lower incidence of respiratory failure after extubation.

Divisions of Newborn Medicine (P. F., C. L., R. P., R. R.) and Research and Biostatistics (E. R., L. C.), Department of Pediatrics, Women's and Children's Hospital, Los Angeles County-University of Southern California (USC) Medical Center, USC School of Medicine, Los Angeles, CA 90033.

Address correspondence and reprint requests to Philippe Friedlich, MD, Division of Neonatology, Children's Hospital Los Angeles, 4650 Sunset Boulevard, Mailstop 31, Los Angeles CA 90027.

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METHODS

This clinical trial was a prospective randomized study in the neonatal intensive care unit at the Los Angeles County-University of Southern California (LAC-USC) Medical Center. The protocol and informed consent forms were approved by the Institutional Review Board of the LAC-USC Medical Center. Written informed consent was obtained from the parents of each patient before enrollment.

Study Population

Mechanically ventilated preterm infants with a birth weight of 500 to 1500 gm, admitted to the LAC-USC neonatal intensive care unit between May 1, 1997 and March 31, 1998, were candidates for the study. Eligibility criteria included the following: (1) Birth weight of 500 to 1500 gm and (2) decision to extubate, as determined by the attending neonatology staff, including the following preextubation ventilatory settings: SIMV rate of $\leq$12 breaths per minute, peak inspiratory pressure (PIP) of $\leq$23 cm H_2O, peak end-expiratory pressure (PEEP) of $\leq$6 cm H_2O, and fraction of inspired oxygen (F_{IO_2}) of $\leq$40%. All patients were clinically stable and had no other significant nonrespiratory conditions at the time of study entry. Exclusion criteria included infants with sepsis, necrotizing enterocolitis, or symptomatic patent ductus arteriosus at the time of extubation as well as infants with the following: nasopharyngeal pathology, such as choanal atresia/stenosis, cleft lip/palate, major congenital malformation, and neuromuscular disorders.

Protocol Design and Randomization

Neonates were randomized to receive NPCPAP or NP-SIMV. The randomization method used a stratified, balanced block procedure of birth weights: 500 to 750 gm, 751 to 1000 gm, 1001 to 1250 gm, and 1251 to 1500 gm. Once the decision was made to extubate the infants, nasopharyngeal prongs (3.0 Fr. silicone binasal pharyngeal airway, Vest Inc., Franklin, WI) were inserted to the level of the posterior pharynx before the removal of the endotracheal tube. The randomization card was then opened, and the endotracheal tube was removed. The nasopharyngeal prongs were secured with sutures to an adhesive tape placed over the philtrum of the upper lip. Patients randomized to the NPCPAP group had the prongs connected to a pressure-limited, time-cycled infant ventilator (Infantstar 950; Infrasonics Inc., San Diego, CA) and received CPAP, adjusted at the discretion of the clinician. Patients in the NP-SIMV group were connected in a similar fashion to the ventilator, but a SIMV rate, PIP, PEEP, and inspiratory time were set. The initial SIMV rate was set at 10 breaths per minute and was adjusted thereafter based on the patient's clinical status. PIP was initially set at the pre-extubation level and adjusted as needed. Initial PEEP was set at 4 to 6 cm H_2O. A long inspiratory time of 0.6 seconds was used to optimize alveolar recruitment. The synchronization of the mechanical breaths was achieved through a trigger sensor applied to the subject's abdomen (Star Sync Abdominal Sensor, Infrasonics Inc.). In both groups, F_{IO_2} was adjusted to maintain oxygen saturation, as measured by pulse oximeter (Novametrix 7100; Willington, CT), at between 92% and 95%. Suctioning of the nasopharyngeal prongs was part of the routine respiratory care when needed. Blood gas analyses were obtained at 1 hour postextubation and subsequently at 6, 12, 24, and 48 hours and as clinically indicated. The infant's clinical condition, vital signs, daily weight, and total enteral and parenteral fluid intake were monitored. A chest radiograph was obtained at 3 to 4 hours postextubation and thereafter as clinically indicated. An orogastric tube to gravity was placed in all patients.

In the NP-SIMV group, the SIMV rate was weaned as tolerated based on clinical and blood gas data down to a rate of no less than four breaths per minute before the nasopharyngeal prongs were removed. Infants assigned to the NPCPAP group were weaned to a PEEP of 4 cm H_2O before removal of the prongs.

Presence of two or more of the following criteria was considered as respiratory failure after extubation: (1) a pH of $\leq$7.25 on two blood gases drawn 30 minutes apart, (2) a change in P_{CO_2} of 25% above pre-extubation value, (3) F_{IO_2} of $\geq$60% to maintain saturation at 92% to 95%, (4) an SIMV rate of $\geq$20 in the NP-SIMV group, (5) a PIP of $\geq$26 cm H_2O in the NP-SIMV group, (6) a PEEP of $\geq$8 cm H_2O, or (7) an apneic episode with bradycardia at $<$100 beats per minute that did not resolve with stimulation and required bag and mask ventilation. No crossover was allowed in the study protocol. Once a patient met criteria for respiratory failure, the study was terminated. The need for reintubation was left to the discretion of the clinician.

Demographics, the length of initial endotracheal intubation, the incidence of therapy failure at 48 hours, and the incidence of possible therapy complications were recorded.

Sample Size and Statistics

A sample size of 55 patients in each group was estimated to be necessary to detect a minimum of 50% reduction in respiratory failure postextubation (using an α error of 0.05 and 80% power). A statistical analysis completed after 41 patients were enrolled demonstrated a statistically significant difference in postextubation respiratory failure between the groups at an α level of 0.016. Based on this significant difference, the study was terminated.

Statistical analyses of data were performed using the SAS System for Windows, Release 6.12 (Cary, NC). The Mann-Whitney *U* test was applied for continuous or ordinal variables to test significant differences between the two treatment groups. Differences in categorical variables were compared using the χ-squared test or Fisher's exact test. A p value of $\leq$0.05 was considered significant.

RESULTS

Between May 1, 1997 and March 31, 1998, 61 patients met study criteria. Informed consent was obtained for 41 infants. We were unable to obtain parental consent before extubation in 20 patients.

Demographic characteristics are displayed in Table 1. Between the NP-SIMV ($n = 22$) and the NPCPAP ($n = 19$) groups, there were no significant differences noted in birth weight, in gestational age, and in the proportion of infants with a size appropriate for their gestational age.

Table 1 Comparison of Demographic Characteristics Between NP-SIMV and NPCPAP Groups

	NP-SIMV ($n = 22$)	NPCPAP ($n = 19$)	p value
Birth weight (grams)	963 ± 57 [535–1490]*	944 ± 43 [640–1285]	0.969
Gestational Age (weeks)	28.0 ± 0.6 [23–32]	27.6 ± 0.6 [23–31]	0.619
Male:female	12:10	11:8	0.829
Amnionitis (%)	14%	27%	0.436
Antenatal steroid (# dose)	0.9 ± 0.2 [0–3]	1.2 ± 0.2 [0–3]	0.321
Cesarean section (%)	77%	79%	1.000
1-min Apgar	4† [1–8]	6† [1–9]	0.227
5-min Apgar	7† [1–9]	7† [5–9]	0.320

*Mean ± standard error [range].
†Median value.

Table 2 summarizes the initial mechanical ventilation characteristics. There were no differences noted between the two groups in terms of indication for first intubation (respiratory distress syndrome versus apnea), mode of initial mechanical ventilation (use of conventional versus high-frequency ventilation), and the number of surfactant doses. Initial mean airway pressures, oxygen requirements, pH, and Pco_2 were similar. Before extubation, incidences of pulmonary interstitial emphysema and pneumothoraces were similar between the two groups.

Patient characteristics and the ventilatory settings for patients at the time of extubation are shown in Table 3. The duration of endotracheal ventilation was 26.3 ± 6 days in the NP-SIMV group and 19.9 ± 3.8 days in the NPCPAP group ($p = 0.793$). Corrected gestational age and weight at extubation were similar. At the time of extubation, aminophylline was used in 82% of the NP-SIMV group and in 90% of the NPCPAP group ($p = 0.668$). All patients were on a pressure-limited, time-cycled ventilator at the time of extubation. Synchronized ventilator rate, PIP, PEEP, and FIo_2 requirements as well as pH and Pco_2 were similar between the two groups before extubation. (Table 3). One patient in each group had low Pco_2 values (18 and 23 mm Hg, respectively) on the last blood gas before extubation. These two patients did not develop respiratory failure during the study and did not require reintubation during their hospital course.

Of the patients randomized to NP-SIMV, 1 of 22 (5%) failed therapy; of the patients randomized to NPCPAP, 7 of 19 (37%) failed therapy at 48 hours postextubation ($p = 0.016$) (Figure 1). The one patient in the NP-SIMV group that failed therapy failed secondary to apnea and bradycardia due to sepsis and required reintubation. The seven patients failed therapy in the NPCPAP group secondary to a pH of ≤7.25 and increasing Pco_2 ($n = 4$) and apnea and bradycardia ($n = 3$) (Figure 1). The mean duration of therapy was 79 hours for the NP-SIMV group (range = 6 to 312) and 51 hours for the NPCPAP group (range = 6 to 214) ($p = 0.1$). One of the seven patients in the NPCPAP who failed therapy required reintubation. The other six patients were rescued outside of the study protocol with NP-SIMV. No other study patients required endotracheal intubation at 1 week postextubation.

No subjects were withdrawn from the study. One case of moderate abdominal distention in the NPCPAP group was noted but was not clinically significant. There were no cases of necrotizing enterocolitis or intestinal perforation in either group during the study period. No significant delays in feeding were noted. In the NP-SIMV group, one patient had a self-resolving episode of nasal bleeding 3 days after discontinuation of the nasal prongs during suctioning of the nares. No other adverse events were noted. All patients had a normal brainstem auditory-evoked response at the time of discharge from the neonatal intensive care unit.

DISCUSSION

In this randomized study, we have shown that patients extubated to the NP-SIMV mode had a significantly lower incidence of respiratory failure compared with the NPCPAP group (5% vs 37%; $p = 0.016$) at 48 hours postextubation.

Successful early extubation and the prevention of reintubation of VLBW infants remain primary treatment goals in caring for this at-risk population. The impetus for these goals is that prolonged intubation with mechanical ventilation is associated with several adverse outcomes, including barotrauma, volutrauma, oxygen toxicity, subglottic stenosis, and nosocomial infections. However, early extubation is associated with its own inherent risks due to residual airway and lung disease, apneic episodes, atelectasis, and a high incidence of postextubation respiratory failure.[9,10]

Various means of achieving successful early extubation have been studied. Among the peri- and postextubation mechanical ventilation modalities studied in the VLBW population are the delivery of supplemental oxygen by hood, nasal cannula, pressure-delivery systems such as nasal CPAP (NCPAP), NPCPAP, pre-extubation endotracheal CPAP, and gradual lowering of the IMV rate. Although some have concluded that NCPAP and NPCPAP facilitate extubation and may help avoid the need for reintubation when compared with postextubation oxyhood administration, others have not.[18–25] Lin et al.[23] compared NCPAP with nasal intermittent positive pressure ventilation at the time of extubation of VLBW infants and found that nasal inter-

Table 2 Comparison of Initial Mechanical Ventilation Characteristics Between NP-SIMV and NPCPAP Groups

	NP-SIMV ($n = 22$)	NPCPAP ($n = 19$)	p value
Intubated for RDS*	82%	90%	0.668
HFOV†	46%	47%	0.902
Surfactant doses	1.4 ± 0.24 [0–3]‡	1.5 ± 0.28 [0–3]	0.685
Initial MAP§ HFOV (cm H_2O)	12.9 ± 0.72 [9.9–17.5]	11.3 ± 0.65 [8.1–13.8]	0.199
Initial MAP SIMV (cm H_2O)	6.7 ± 0.35 [5–8]	7.5 ± 0.42 [5–8.8]	0.094
Initial FiO_2 (%)	57 ± 7 [21–100]	49 ± 6 [21–100]	0.494
Initial pH	7.31 ± 0.03 [6.97–7.52]	7.36 ± 0.03 [7.08–7.61]	0.488
Initial PCO_2 (mm Hg)	40 ± 3 [22–96]	35 ± 2 [15–51]	0.395
History of PIE¶	14%	11%	1.000
Pneumothorax	14%	5%	0.610
Length of ventilation (days)	26.3 ± 6.1 [1–120]	19.9 ± 3.8 [1–54]	0.793

*RDS = respiratory distress syndrome.
†HFOV = high-frequency oscillatory ventilation.
‡Mean ± standard error [range].
§MAP = mean airway pressure.
||PIE = pulmonary interstitial emphysema.

Table 3 Comparison of Extubation Characteristics Between NP-SIMV and NPCPAP Groups

	NP-SIMV ($n = 22$)	NPCPAP ($n = 19$)	p value
Extub* DOL (days)	26.3 ± 6.1 [1–120]†	19.9 ± 3.8 [1–54]	0.793
	18.5‡	21.0‡	
Extub GA (weeks)	31.7 ± 0.5 [28–40]	30.5 ± 0.5 [27–34]	0.137
	31.5‡	31.0‡	
Extub weight (grams)	1303 ± 96 [930–2970]	1187 ± 46 [910–1500]	0.657
	1197.5‡	1175.0‡	
Extub vent rate (bpm)§	7.7 ± 0.32 [4–10]	8.2 ± 0.31 [6–11]	0.361
Extub PIP (cm H_2O)	17.3 ± 0.53 [13–23]	16.6 ± 0.63 [13–22]	0.458
Extub PEEP (cm H_2O)	4.1 ± 0.13 [3–5]	4.2 ± 0.18 [3–6]	0.668
Extub FiO_2 (%)	23.1 ± 0.69 [21–31]	23.9 ± 1.15 [21–40]	0.729
Extub pH	7.37 ± 0.01 [7.30–7.48]	7.37 ± 0.01 [7.29–7.50]	0.627
Extub PCO_2 (mm Hg)	42.9 ± 2.21 [18–61]	44.8 ± 2.22 [23–59]	0.505

*Extub = extubation.
†Mean ± standard error [range].
‡Median value.
§bpm = breaths per minute.

mittent positive pressure ventilation was more effective than NCPAP in reducing the frequency of apnea and bradycardia. Although NCPAP and NPCPAP are accepted modalities in the management of extubated premature infants in many centers, there is still controversy in their efficacy for preventing reintubation.[15,18–22,25] Discrepancies in extubation success associated with the use of NCPAP and NPCPAP can be explained by several factors, including differences in the definitions of therapy success or failure, inadequate study sample size and power, the level of positive pressure applied through the NCPAP or NPCPAP prongs, and differences in the definition and intervention for postextubation respiratory failure.

A review of the current literature as well as our own experience revealed a reintubation rate in premature infants of between 25% and 40%.[20–22] In 1995, we observed that some premature infants placed on NPCPAP upon extubation who developed early signs of respiratory failure could be adequately ventilated with the addition of mechanical breaths (i.e., SIMV) delivered through the nasopharyngeal prongs (NP-SIMV). In our initial pilot study evaluating this method of ventilation as a "rescue" mode, we were able to rescue and avoid reintubation of 70% of these high-risk newly extubated premature infants.[24]

Based on our present data, VLBW infants directly extubated to NP-SIMV were 1.5 times more likely to avoid respiratory failure com-

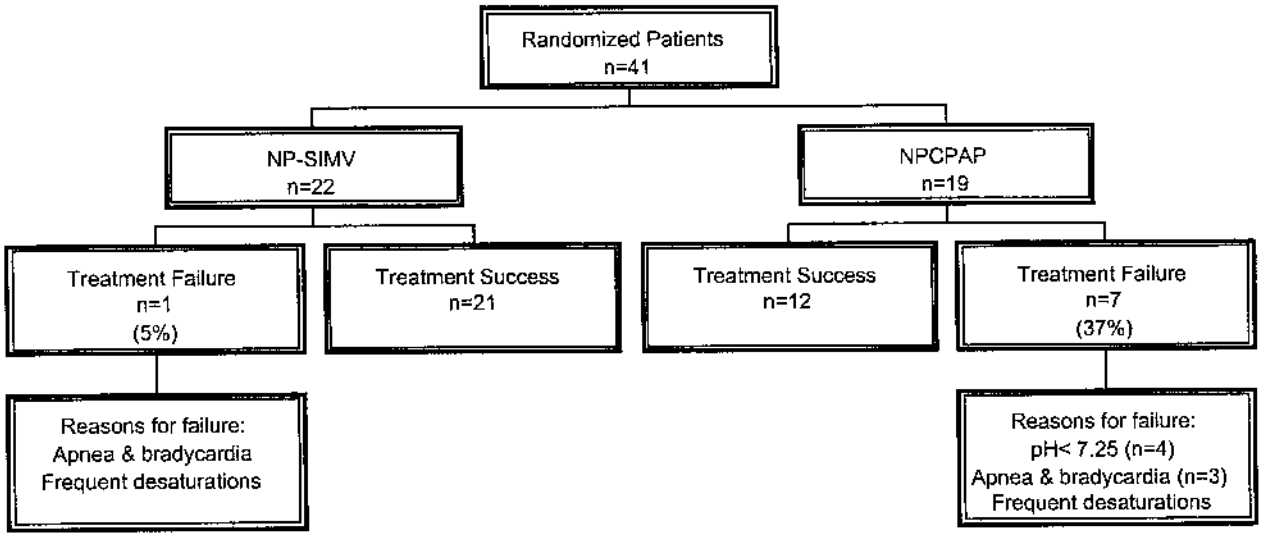

Figure 1. Treatment outcome between NP-SIMV and NPCPAP groups.

pared with VLBW infants directly extubated to NPCPAP. These results can not be explained based on differences in severity of initial illness and associated complications, time to extubation, ventilatory management before extubation, weight, age, or nutritional status at the time of extubation.

NCPAP and NPCPAP have been described previously in the literature as techniques for weaning patients off of mechanical ventilation following extubation.[20] Proponents of these weaning techniques have noted that preservation of functional residual capacity, a reduction in alveolar atelectasis, and a reduction in episodes of apnea and bradycardia are all possible underlying physiologic benefits by which NCPAP or NPCPAP succeed. We believe that the addition of a higher intermittent distending pressure above PEEP as well as increased flow delivery in the upper airway as provided by our NP-SIMV technique may indeed further stabilize a borderline functional residual capacity, reduce dead space, as well as prevent atelectasis in the postextubation period. Recently, Kiciman et al.[26] have demonstrated a decrease in thoracoabdominal motion asynchrony in newborns ventilated with nasal IMV. The authors concluded that nasal IMV decreases flow resistance through the nasal prongs and improves the stability of the chest wall, resulting in improved pulmonary mechanics.[26]

In our study, few adverse effects accompanied the NP-SIMV method of assisted ventilation. One case of moderate non-clinically significant abdominal distention and one case of self-resolved epistaxis were noted. No evidence of significant abdominal distention, necrotizing enterocolitis, gastrointestinal perforation, pulmonary airleak, upper airway injury including erosion of the nasal septum, or cardiovascular effect was seen in our study population but are described in the literature.[27,28] The theoretical adverse effects associated with administration of high inspiratory pressure at the level of the nasopharynx, including hearing impairment, middle ear infection, and chronic inflammation of nasopharyngeal mucosa, are of concern. During the study period, mucous plugging of the nasopharyngeal prongs was not preventable but was easily corrected with occasional suctioning. Auditory screening at the time of discharge was normal in all subjects, and is reassuring.

CONCLUSION

We have demonstrated in this prospective, randomized trial that NP-SIMV applied immediately upon extubation of VLBW infants is significantly more effective in preventing respiratory failure compared with NPCPAP alone. We believe that further investigation of this technique to elucidate unanswered questions with regard to long-term safety as well as pulmonary function is warranted.

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